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Office européen des brevets



(11) Publication number: **0 409 383 B1**

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification :
06.04.94 Bulletin 94/14

(51) Int. Cl.⁵: **A61K 31/565, A61K 47/32,
A61L 15/44**

(21) Application number: **90305377.5**

(22) Date of filing: **18.05.90**

(54) **Estradiol compositions and methods for topical applications.**

(30) Priority: **21.07.89 IL 91067
08.01.90 US 461676**

(43) Date of publication of application :
23.01.91 Bulletin 91/04

(45) Publication of the grant of the patent :
06.04.94 Bulletin 94/14

(84) Designated Contracting States :
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(56) References cited :
**EP-A- 0 054 279
EP-A- 0 181 970
EP-A- 0 364 211
EP-A- 0 371 496
WO-A-89/07951**

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EP 0 409 383 B1

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Description

This invention relates to novel compositions of matter for topical application to humans and methods for providing therefrom a controlled dosage of 17- β -estradiol. The novel compositions comprise estradiol and a polymer in a form adapted for the slow and gradual release of the medicament so that the concentration of drug in the blood plasma of the patient is maintained within levels desirable for optimum clinical efficacy.

Knowledge of the endocrinological role of estradiol dates from the early part of this century. Its relation to the menstrual cycle was established in the 1920s and its chemical structure was elucidated in the 1930s.

When the ovaries do not function properly due to age, i.e. menopause, or disease, or have been removed, the consequent lack of endogenous estradiol may produce a number of symptoms, such as hot flushes, pain and increased hypocalcemia, eventually leading to osteoporosis.

One way of avoiding or alleviating these symptoms is by estrogen replacement therapy, i.e. by giving a compensatory dose of estrogen to the patient. This treatment is not without danger, since it has been established by various researchers that in women taking exogenous estrogens, there is an increased risk of endometrial cancer, estimated to be between 4.5 to 13.9 times greater than in women not taking exogenous estrogen. The risk is related to dosage and duration of use. Other side effects due to the intake of estradiol may be cholelithiasis (gall bladder disease) and thromboembolic disease due to increase in lipoproteins and triglycerides in the blood.

As a result of the increase in the average age of the human population during the last few decades, there are more female patients suffering from post-menopausal symptoms and osteoporosis and, therefore, there is a growing need for this form of therapy. However, due to the sometimes dangerous side effects mentioned hereinbefore, treatment requires a very fine tuning of the dosage, i.e. the blood levels of the drug are kept at the minimum required for clinical efficacy.

The concentration of estradiol required for clinical effectiveness has been shown to be between 50 and 120 picograms per milliliter (pg/l) of plasma. At 60 pg/l a reduction of about 50% of the hot flushes was observed and at about 120 pg/ml they totally disappeared.

Various methods are in use or have been proposed for the estradiol replacement therapy, e.g. tablets, aqueous suspensions for injection, implants and patches for transdermal application.

Oral therapy, using tablets, is most convenient for the patient but the effect is rather short since the half-life of estradiol in the plasma is only one hour and up to three doses per day may be required to maintain therapeutically effective levels. The first pass inactivation of estradiol is very high, its oral availability being only about 30%. This leads to accumulation in the body of large quantities of estrone and other estrogens.

Resetarits et al (International Journal of Pharmaceutics, 2, 113-123 (1979) reported that the dissolution rate of estradiol-polyvinylpyrrolidone "coprecipitates", prepared by dissolving both components in ethanol and subsequently removing the solvent in vacuo, was appreciably higher than that of microcrystalline estradiol. There was no evidence that estradiol and polyvinylpyrrolidone formed complexes in the solid state and it was concluded that in the "coprecipitate" the estradiol exists in a more water-soluble, high energy form of the drug. It was suggested that this may increase the systemic availability of the estradiol and reduce the extensive pre-systemic metabolism after oral administration.

The use of parenteral injections and implants or pellets while avoiding the first pass loss, is much less convenient for the patient and, therefore, the use of these forms of therapy is not popular.

The administration of estradiol from a dosage form adapted for nasal delivery, e.g. solutions, suspensions, gels and ointments, is disclosed in U.S. Patent No. 4,383,993. The dosage form consists of estradiol and a pharmaceutically acceptable nasal carrier, e.g. a mixture of water, an emulsifier and, if desired, a gelling agent.

Estradiol, like other estrogens, is readily absorbed through the skin and since, as indicated hereinbefore, very low concentrations (around 100 pg/ml) are required for clinical efficacy, this renders it an excellent candidate for transdermal application. Schenkel, Barlier, Riera and Barner (Journal of Controlled Release, 4, 195-201 (1986) have shown that transdermal application of estradiol to different body sites results in comparable absorption.

Patches for transdermal application generally involve membrane-control of the delivery of the drug. U.S. Patent No. 4,379,454 discloses an adhesive patch in which estradiol and ethanol simultaneously permeate through an ethylene-vinyl acetate copolymer membrane from a gelled estradiol-ethanol mixture which is in contact with the membrane. The ethanol enhances the rate of percutaneous absorption of the estradiol.

Transdermal delivery systems for estradiol have been reviewed by Good, Powers, Campbell and Schenkel (Journal of Controlled Release, 2, 89-97 (1985) and Guy and Hadgraft (Journal of Controlled Release, 4, 237-251 (1987).

The factors affecting the diffusion of steroids, including estradiol, through crosslinked polydimethylsiloxane membranes have been reported by Lacey and Cowsar in "Controlled Release of Biologically Active

Agents", Tanquary and Lacey, eds, Plenum Press, New York, pp. 117-144 (1974).

The present invention is directed towards improvements in the transdermal delivery of estradiol wherein compositions containing the steroid, upon topical application, will provide a slow and sustained release of the estradiol so as to maintain the desired level of the drug in the blood of the patient. This is accomplished by the incorporation of uncrosslinked, water-insoluble vinylpyrrolidone copolymers in the compositions.

The use of water-soluble polyvinylpyrrolidone in conjunction with various medicaments has been disclosed in a number of patents. Thus, German DOS 2,301,664 and British Patent No. 1,427,881 disclose the prolongation of the storage stability of nitroglycerin by the addition of polyvinylpyrrolidone. U.S. Patent No. 4,091,091 describes the stabilization of nitroglycerin against tablet-to-tablet migration by the incorporation of water-soluble polyvinylpyrrolidone in the mixture of a water-soluble excipient and nitroglycerin, while retaining the rapid solubility of the tablet in the mouth.

The release of nitroglycerin as a result of the water-solubility of vinylpyrrolidone homopolymer or copolymers has also been utilized in an antianginal film or plate. Thus, British Patent Application No. 2021610A discloses that a thin film containing nitroglycerin, a water-soluble homopolymer or copolymer of acrylamide and/or vinylpyrrolidone and, optionally a dispersed solid fat, is applied to a site in the mouth and releases the medicament at a rate which is dependent upon the rate of solution of the polymer.

The prior art teaches that water-soluble vinylpyrrolidone homopolymer complexes with nitroglycerin in a solid tablet or film and reduces the volatility and migration of the medicament without reducing the availability of the drug in an aqueous environment.

U.S. Patent No. 4,482,534 discloses that the incorporation of water-insoluble vinylpyrrolidone homopolymer or copolymers in an ointment, gel or film containing nitroglycerin provides increased stability and reduced volatility of the nitroglycerin, while permitting slow release of the drug when applied topically to the skin.

The use of water-soluble polyvinylpyrrolidone in conjunction with medicaments other than nitroglycerin has been disclosed in a number of patents. Thus, U.S. Patent No. 3,972,995 discloses a buccal dosage form in which the water-soluble homopolymer functions as a binder in an adhesive layer. U.S. Patent No. 3,214,338 discloses a topical ointment in which the water-soluble homopolymer is added to an emulsifiable polyvinyl acetate powder. U.S. Patent No. 3,803,300 discloses a film-forming ointment containing water-soluble vinylpyrrolidone homopolymer or copolymers. U.S. Patent No. 3,287,222 discloses the use of the homopolymer as a water-soluble plasticizer in an impregnating solution for a synthetic fiber medical dressing. U.S. Patent No. 4,210,633 discloses a water-soluble medicated film containing the water-soluble homopolymer. U.S. Patent No. 3,608,070 discloses a surgical dressing which is an ointment containing a vinylpyrrolidone copolymer, a thixotropic agent, a water-soluble plasticizer and a solvent such as aqueous ethanol. The film formed on drying the ointment is readily soluble in water. U.S. Patent No. 2,776,924 discloses the use of water-soluble polyvinylpyrrolidone to inhibit adverse reactions from therapeutic agents in topical application.

In these prior art disclosures with medicaments other than nitroglycerin, vinylpyrrolidone polymers are used because of their film-forming ability and/or water solubility. The rapid solubilization of the polymer results in rapid release of the medicament.

The prior art discloses that the use of water-insoluble, crosslinked polyvinylpyrrolidone also promotes the rapid release of medicament. Thus, British Patent No. 1,380,171 discloses the use of crosslinked, water-insoluble polyvinylpyrrolidone in medicinal tablets containing a drug, to promote rapid disintegration of the tablet in aqueous fluids and increase the availability of the drug. Examples are provided which illustrate that the presence of water-insoluble polyvinylpyrrolidone results in more rapid disintegration and release of the drug as compared with the water-soluble polymer. German Patent Application 2,634,004 discloses the use of crosslinked, insoluble polyvinylpyrrolidone as a carrier material for poorly soluble medicaments in order to accelerate the release thereof when administered orally. German Patent Application 1,467,792 discloses the use of crosslinked polyvinylpyrrolidone as a disintegration agent to increase the rate of disintegration of a tablet to promote the extremely rapid release of the drug therein in the digestive tract.

SUMMARY OF THE INVENTION

The prior art teaches that water-soluble polyvinylpyrrolidone complexes with nitroglycerin in a solid tablet or film to reduce the volatility without reducing the availability of the drug, when the composition is placed in contact with water. The prior art also teaches that the presence of water-insoluble polyvinylpyrrolidone promotes even more rapid release of a medicament.

The prior art further teaches that estradiol, in contrast to nitroglycerin, does not complex with water-soluble polyvinylpyrrolidone in the solid state and is more water-soluble in the presence than in the absence of the polymer.

Surprisingly, it has now been discovered that the incorporation of an uncrosslinked, water-insoluble vinyl-

pyrrolidone copolymer in an ointment, gel or film containing estradiol permits slow release of the drug when applied topically to the skin.

It has further been discovered that the delivery of estradiol from a composition which contains a water-insoluble vinylpyrrolidone copolymer and is applied directly to the skin without an intervening membrane, maintains blood levels of the drug at the concentration required for clinical efficacy.

It has further been discovered that ointments with sustained release characteristics can be prepared by the admixture of a dispersion or solution of a water-insoluble vinylpyrrolidone copolymer with an estradiol solution and a conventional hydrophobic base such as vasoline, and lanolin.

It has further been discovered that films with sustained release characteristics can be prepared from a solution containing a water-insoluble vinylpyrrolidone copolymer and estradiol, wherein the solution is applied *per se* or after thickening.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, it has now been found that important advantages and improvements over prior art compositions containing 17β -estradiol and methods of topical application thereof can be obtained by admixture with an uncrosslinked, water-insoluble vinylpyrrolidone copolymer.

Water-insoluble copolymers of vinylpyrrolidone, which may be used in the practice of this invention, may be prepared by the copolymerization of vinylpyrrolidone with one or more appropriate comonomers in the proportions which yield water-insoluble, uncrosslinked copolymers. Suitable comonomers include acrylic esters, methacrylic esters, vinyl esters, crotonic esters, vinyl ethers, maleic half esters and diesters, vinylene carbonate, styrene, allyl esters, allyl ethers, etc. Other comonomers which are capable of copolymerizing with vinylpyrrolidone and are well known to those skilled in the art may also be used. Toxicological considerations restrict the choice of monomers to those which yield copolymers having a demonstrated lack of toxicological side-effects on topical application to the skin.

The acrylic, methacrylic, crotonic and maleic esters which may be used in the preparation of the water-insoluble vinylpyrrolidone copolymers which are effective in the practice of the present invention, include the esters of C_1 - C_{40} linear, branched or cyclic alkanols, aralkanols, phenols and substituted phenols. The copolymers of vinylpyrrolidone and the acrylic, methacrylic, crotonic and maleic esters may be made by copolymerization of vinylpyrrolidone with the appropriate ester or by esterification of copolymers of vinylpyrrolidone and acrylic, methacrylic, crotonic and maleic acid or anhydrides, with the appropriate hydroxy-containing compound. Unesterified carboxylic acid functionality may be retained in the copolymer.

The vinyl esters and allyl esters which may be used in the preparation of the water-insoluble vinylpyrrolidone copolymers which are useful in the practice of this invention, include the esters of C_1 - C_{40} linear, branched or cyclic aliphatic, araliphatic or aromatic carboxylic acids. The copolymers of vinylpyrrolidone and the vinyl esters may be prepared by copolymerization of vinylpyrrolidone with the appropriate vinyl ester or by transesterification of copolymers of vinylpyrrolidone and vinyl acetate or other vinyl esters or by esterification of hydrolyzed copolymers of vinylpyrrolidone and vinyl acetate or other vinyl esters. The copolymers of vinylpyrrolidone and allyl esters may also be prepared either by direct copolymerization or by transesterification or esterification, analogous to the preparation of vinyl ester copolymers with vinylpyrrolidone.

Graft copolymers made by grafting vinyl monomers onto polyvinylpyrrolidone may also be used, e.g. graft copolymers of polyvinylpyrrolidone with acrylic esters, methacrylic esters, styrene, and vinyl acetate.

The water-insoluble copolymers of vinylpyrrolidone which may be used in the practice of the present invention, may be prepared by any of the conventional methods known in the art, including bulk, solution, emulsion, suspension or dispersion polymerization, with appropriate free radical catalysts such as peroxygen compounds, azo compounds, redox systems, radiation and other catalytic techniques for initiating free radical polymerization. Since the method of polymerization is not an integral part of the practice of the present invention, any suitable method known to those skilled in the art may be used.

The amount of one or more comonomers in the water-insoluble vinylpyrrolidone copolymers which are useful in the practice of the present invention, may be varied from 0.1 to 90% by weight. The actual amount is determined by the nature of the comonomer and the concentration necessary to produce a water-insoluble copolymer.

The drug used in the practice of the present invention may be 17β -estradiol or its esters such as estradiol benzoate, cypionate, valerate or other derivatives such as ethinylestradiol. However, the preferred drug is 17β -estradiol.

The estradiol compositions which are useful in the practice of the present invention and provide sustained release of the medicament, may be prepared by dissolving or dispersing the water-insoluble vinylpyrrolidone copolymer in a solvent such as isopropanol, ethanol or an alcohol-water mixture, and admixing the polymer

solution or dispersion with estradiol per se or as an estradiol solution in alcohol.

The solution of uncrosslinked, water-insoluble vinylpyrrolidone copolymer and estradiol, in the presence or absence of an excipient, may be cast on a suitable surface and the solvent evaporated under ambient pressure or in vacuo, at ambient or slightly elevated temperature. The resultant film on the substrate surface or
5 after removal from the substrate, contains estradiol and may be cut into strips or tapes which can be affixed to the skin of a patient for sustained release of the medicament.

The solution of uncrosslinked, water-insoluble vinylpyrrolidone copolymer and estradiol may be applied directly to the skin of the patient and permitted to evaporate to form a film thereon, containing estradiol. The latter is slowly released from the film and absorbed into the skin of the patient.

10 The solution of vinylpyrrolidone copolymer and estradiol may be conveniently applied to the skin using an aerosol formulation containing one or more low boiling propellants. Although fluorocarbon propellants such as trichloromonofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane are particularly effective, other propellants well known to those skilled in the art may be used. The solution of estradiol and water-insoluble vinylpyrrolidone copolymer in ethanol may be pressurized in an aerosol can with a propellant. In order
15 to control the amount of polymer and estradiol applied to the skin, it is advantageous to use a metering valve which delivers precise quantities of solution. When applied in this manner, the propellant and solvent quickly evaporate leaving a dry film of controlled estradiol content covering the desired area of skin.

A gel or thickened solution of estradiol and water-insoluble vinylpyrrolidone copolymer may be applied with greater control to a restricted area of skin than a low viscosity solution. The solution may be thickened by the addition of a small amount of a soluble high molecular weight inert polymer or a thickener of the type well known to those skilled in the art. High surface area inorganic materials such as finely divided fumed silica are particularly effective thickeners. The addition of a small amount of such a material results in a marked increase in the viscosity of the solution. The resultant gel or thickened solution exhibits thixotropy and flows readily during application but does not spread after application to the skin. The large surface area of the thickener increases the rate of evaporation of the solvent and contributes to rapid drying and film formation. The estradiol
25 is slowly released and absorbed into the skin of the patient. At the end of the desired treatment period, or sooner if undesirable reaction to the estradiol is noted, the film may be removed by rubbing with soap and water or alcohol.

30 The gel or thickened solution may be applied to the skin in a pre-measured amount from a tube or a roll-on dispenser.

A solution or dispersion of uncrosslinked, water-insoluble vinylpyrrolidone copolymer and estradiol, in the absence or presence of an excipient, may be applied to a porous or open-structured substrate such as gauze, bandage tissue or paper, and upon evaporation of the solvent, provides an impregnated structure containing estradiol, which is released over an extended period of time when applied topically to the skin of a patient.

35 The solution or dispersion of water-insoluble vinylpyrrolidone copolymer and estradiol may be mixed, with stirring, with one or more ointment bases, such as petrolatum, vasoline, lanolin, stearin, spermaceti wax or other waxy or fatty material. The ointment may be applied directly to the skin of a patient or may be coated on a carrier such as a bandage or polymeric tape for topical application to the skin of a patient. The estradiol is slowly released and absorbed into the skin of the patient over an extended period of time.

40 Although the vinylpyrrolidone copolymer is water-insoluble, the hydrophilicity of the vinylpyrrolidone units contained therein results in moisture absorption, e.g. from perspiration on the skin of the patient, and extraction of the estradiol from the composition, followed by absorption of the drug into the skin. The rate of extraction may be varied over a wide range and is dependent upon the concentration of vinylpyrrolidone in the copolymer.

45 The concentration of water-insoluble vinylpyrrolidone copolymer and estradiol in the compositions of the present invention, may be varied over a wide range, depending upon the desired release rate. The estradiol concentration may range from about 0.01% to about 1% of the total weight of the composition, while the concentration of the water-insoluble vinylpyrrolidone copolymer may range from about 5 to about 5000% of the weight of the estradiol.

50 The following examples are non-limiting illustrative embodiments of the compositions and methods of the present invention. Variations thereof will be obvious to those skilled in the art.

EXAMPLE I

55 The emulsion copolymerization of 66.7 parts of N-vinylpyrrolidone (VP) and 28.6 parts of lauryl methacrylate (LM) was carried out in 200 parts of water containing 5 parts of sodium stearate and 1.25 parts of 30% hydrogen peroxide as catalyst. The mixture was heated with stirring and the polymerization was carried out at 75°C for about 10 hours. The conversion was 92%. The emulsion was spray dried at about 210°C to yield a fine, off-white powder. The nitrogen content of the copolymer was 8.6%, indicating a VP content of 68%.

A gel base was prepared by dissolving 20 parts of the VP/LM copolymer in 64 parts of anhydrous ethanol with stirring at room temperature. To the above solution were added 6 parts of glycerin, 3 parts of high molecular weight polyvinylpyrrolidone and 6 parts of fumed silica. Estradiol-containing gels were prepared by mixing 0.1 or 0.25 parts of 17 β -estradiol into 100 parts of the gel base. The resultant smooth gels were applied to the skin of patients from a tube by means of a graduated piece of cardboard. The gels dried completely after 3 minutes producing soft, pliable estradiol-containing films.

EXAMPLE II

An emulsion polymerization was carried out using the following ingredients, in parts by weight:

	Water	22,100
15	Stearic acid	440
	Ammonium hydroxide (25%)	192
	Isopropanol	112
20	N-Vinylpyrrolidone	8,064
	Lauryl methacrylate	3,456
25	Sodium metabisulfite (6% aq. solution)	425
	Hydrogen peroxide (30%)	156

All of the ingredients except the sodium metabisulfite solution were charged into a stainless steel reactor equipped with heating jacket, condenser and mechanical stirrer. The bisulfite solution was added slowly over 5 hours, while maintaining the temperature at 75°C with stirring. The reaction was then continued with stirring for an additional 4 hours at 75°C and then the emulsion was permitted to cool to room temperature. The solids content was 32.5%, representing 94% conversion. The emulsion was diluted to 20% solids and spray dried at 210°C to yield a fine, off-white powder which had a nitrogen content of 8.7%, equivalent to a VP content of 69%.

A gel was prepared by vigorously mixing the following ingredients, in parts by weight:

	VP/LM copolymer	11.0
	Cetyl alcohol	4.0
40	Propylene glycol	5.5
	Isopropyl myristate	2.8
	Magnesium stearate	1.0
	Sodium stearate	3.8
	Fumed silica	7.0
45	Ethanol	68.0

The resultant gel had a viscosity of 30,000 - 40,000 cps.

Estradiol-containing gels were prepared by mixing 100 parts of the base gel with 0.05 to 1.0 part of estradiol. The resultant formulation was packed into aluminum tubes and applied to the skin of various menopausal patients having very low endogenous estradiol. The application of 1.5 grams of the gel was made once a day.

The estradiol content (E2) in the plasma was determined periodically.

Patient	A	B	C	D
Estradiol in gel, %	0.05	0.1	0.5	1.0
Estradiol in plasma, pg/ml				
Initial	22	<10	37	25
After 3 days	46	64	67	-
After 5 days	-	-	-	83
After 21 days	-	-	70	-

EXAMPLE III

An emulsion polymerization was carried out with the following charge, in parts by weight:

Water	23,042
Emulsifier*	460
Ammonium hydroxide (25%)	75
N-Vinylpyrrolidone	9,288
Lauryl methacrylate	3,981
Hydrogen peroxide (30%)	339
Sodium metabisulphite	53
Water	979

The first six ingredients were charged into the reactor and the sodium metabisulfite solution was added over 10 hours while the temperature was maintained at 75°C, as described in Example II. After 11 hours the conversion was 96.2%. The emulsion was spray dried and the fine powder had a VP content of 66.1%. After the powder was placed in an oven for 24 hours at 90°C, the free monomer content was found to be 0.03% VP and 0.23% LM.

A gel was prepared from the following ingredients, in parts by weight:

VP/LM copolymer	7.0
Hydroxypropylcellulose	1.0
Cetyl alcohol	1.9
Propylene glycol	1.0
Isopropyl myristate	1.4
Magnesium stearate	0.5
Sodium stearate	1.5
Fumed silica	2.0
Ethanol	83.7

Gels were prepared by mixing 100 parts of the base gel with either 0.5 or 1.0 part of 17 β -estradiol. The resultant gel was packed in aluminum tubes for clinical studies.

The gel containing 1.0% estradiol was applied once a day using a graduated cardboard to a group of menopausal patients. The dosage varied from 0.5 to 1.5 grams of gel per application. The initial and final levels of estradiol in the plasma were determined.

*Ammonium salt of sulfated ester of alkylphenoxypoly(ethyleneoxy)ethanol (Alipal CO436) (registered trademark)

	Patient	Daily Dose (grams)	Time (days)	Estradiol, pg/ml	
				Initial	Final
5	1	1.5	9	25	83
	2	1.5	3	23	111
10	3	0.5	9	20	70
	4	1.5	19	20	11
15	5	1.5	16	20	200
	6	0.5-1.5	5	25	47
	7	0.5-1.5	5	20	86
20	8	0.5-1.5	5	22	98

EXAMPLE IV

25

The solution copolymerization of 64 parts of N-vinylpyrrolidone (VP) and 36 parts of 2-ethylhexyl acrylate (EHA) was carried out in 100 ml of isopropanol using one part of lauroyl peroxide as catalyst. The catalyst was added as part of the initial charge and the polymerization was carried out under reflux, with stirring over a period of 12 hours. The conversion was 95%. The copolymer solution was cast on a sheet of polytetrafluoroethylene, air dried for several hours and then dried in an air oven at 60°C. The nitrogen content of the product was 8.4% indicating a VP content of 66%.

30

A gel was prepared from the VP/EHA copolymer using the recipe shown in Example III. The base gel was mixed with 1.0 part of 17 β -estradiol per 100 parts of base gel and charged into a roll-on dispenser.

35

Application of the estradiol-containing gel to the skin of menopausal patients at a dosage of 1.5 grams per day maintained the estradiol content of the blood plasma at 50 to 150 pg/ml.

EXAMPLE V

40

The gel containing 1% 17 β -estradiol, prepared in accordance with the recipe in Example III, was packed into roll-on plastic containers and tested on patients immediately after hysterectomy plus bilateral salpingo-oophorectomy.

An 0.8 gram dosage of the gel was applied to the skin of the patients on a daily basis and the treatment was continued for a period of 1 to 2 years.

45

	Patient	Treatment Time, years	Estradiol in plasma, pg/ml	
			Range	Mean
50	Menopause	(A) 2	50-100	80
	Surgical menopause	(B) 2	100-250	150
	Surgical menopause	(C) 1	60-150	120
55	Menopause	(D) 1	40-150	110

EXAMPLE VI

A gel base was prepared from VP/LM copolymer, in accordance with Example I. Separately, a gelatinous mixture was prepared from 65 grams of polyethylene glycol with a molecular weight of 300 with 35 grams of polyethylene glycol with a molecular weight of 4000.

VP/LM copolymer gel bases were mixed with estradiol benzoate (0.5%) (A) and ethinylestradiol (0.01%) (B). Similar compositions were prepared by mixing the polyethylene glycol gel with 0.5% estradiol benzoate (C) and 0.01% ethinylestradiol (D).

The rate of diffusion of the estradiol derivatives through a skin membrane was measured in a standard diffusion cell, using isotonic saline as the reception solution. Preparations A and B containing the VP/LM copolymer showed rates of diffusion about one order of magnitude lower than the corresponding copolymer-free preparations C and D.

Claims

1. A composition for the sustained transdermal administration of at least one estrogen, comprising an ointment base, gel, or film comprising at least one estrogen and a water-insoluble vinylpyrrolidone copolymer containing at least 10% by weight vinylpyrrolidone, wherein the estrogen concentration is within the range of 0.01% to 1% of the total weight of the composition.
2. The composition of claim 1, wherein said at least one estrogen comprises an estrogen selected from estradiol, ethinylestradiol and estradiol esters and wherein said water-insoluble vinylpyrrolidone copolymer is uncrosslinked.
3. The composition of claims 1 or 2, wherein the vinylpyrrolidone copolymer contains units derived from an unsaturated acid selected from acrylic acid, methacrylic acid, crotonic acid, maleic acid and the corresponding anhydrides.
4. The composition of claim 3, wherein the ester is selected from the acrylic esters of C₁ to C₄₀ linear alkanols, the acrylic esters of C₁ to C₄₀ branched alkanols, the methacrylic esters of C₁ to C₄₀ linear alkanols and the methacrylic esters of C₁ to C₄₀ branched alkanols.
5. The composition of claim 4, wherein the ester is lauryl methacrylate or 2-ethyl-hexyl acrylate.
6. The composition of claim 2, wherein said vinylpyrrolidone copolymer comprises units derived from an ester of a saturated acid selected from the vinyl and allyl esters of C₁ to C₄₀ carboxylic acids.
7. The composition of claim 6, wherein the ester is vinyl acetate.
8. The composition of claim 2, wherein said vinylpyrrolidone copolymer comprises vinylpyrrolidone and styrene.
9. The composition of any one of claims 1, 2, 3 or 6, wherein the estrogen and water-insoluble vinylpyrrolidone copolymer are combined with an ointment base.
10. A bandage, gauze or tape impregnated or coated with the composition of any preceding claim.
11. The composition of any one of claims 1, 2 or 6, wherein the estrogen and water-insoluble vinylpyrrolidone copolymer are combined with a solvent and a thickener to generate a gelled composition.

Patentansprüche

1. Eine Mischung/Zubereitung zur nachhaltigen transdermalen Verabreichung/ Anwendung wenigstens eines Östrogens, bestehend aus einer Salbenbasis, einem Gel oder Film, der wenigstens ein Östrogen und ein wasserunlösliches Vinylpyrrolidon-Copolymer mit wenigstens 10 Gew.% Vinylpyrrolidon enthält, wobei die Östrogen-Konzentration 0,01 Gew.% bis 1 Gew.% des Gesamtgewichts der Zubereitung beträgt.

2. Die Mischung bzw. Zubereitung nach Anspruch 1, wobei das wenigstens eine Östrogen ausgewählt ist aus Estradiol, Ethinylestradiol und Estradiolestern, und wobei das wasserunlösliche Vinylpyrrolidon-Copolymer unvernetzt ist.
- 5 3. Mischung bzw. Zubereitung nach Anspruch 1 oder 2, wobei das Vinylpyrrolidon-Copolymer Einheiten bzw. Bestandteile enthält, die hergeleitet ist bzw. erhalten wurde von einer ungesättigten Säure, ausgewählt aus Acryl-Säure, Methacryl-Säure, Croton-Säure, Maleic-Säure und den entsprechenden Anhydriden.
- 10 4. Das Präparat nach Anspruch 3, wobei der Ester ausgewählt ist aus Acrylestern mit C₁ bis C₄₀ linearen Alkanolen, Acrylestern mit C₁ bis C₄₀ verzweigten Alkanolen, methacrylischen Estern mit C₁ bis C₄₀ linearen Alkanolen und methacrylischen Estern mit C₁ bis C₄₀ verzweigten Alkanolen.
5. Das Präparat nach Anspruch 4, wobei das Ester Laurylmethacrylat oder 2-Ethyl-hexyl-acrylat ist.
- 15 6. Die Mischung/Zubereitung nach Anspruch 2, wobei das Vinylpyrrolidon-Copolymer Einheiten umfaßt, die abgeleitet sind von Estern einer gesättigten Säure, ausgewählt aus Vinyl- und Allylestern von C₁ bis C₄₀ Carboxyl-Säuren.
7. Mischung/Zubereitung gemäß Anspruch 6, wobei das Ester Vinylacetat ist.
- 20 8. Mischung/Zubereitung gemäß Anspruch 2, wobei das Vinylpyrrolidon-Copolymer Vinylpyrrolidon und Styren enthält.
9. Mischung/Zubereitung nach einem der Ansprüche 1, 2, 3 oder 6, wobei das Östrogen und wasserunlösliches VinylpyrrolidonCopolymer mit einer Salbenbasis kombiniert sind.
- 25 10. Eine Bandage, Gaze oder Band, imprägniert oder beschichtet mit einer Mischung/Zubereitung gemäß einem der vorhergehenden Ansprüche.
- 30 11. Eine Mischung nach Anspruch 1, 2 oder 6, wobei das Östrogen und wasserunlösliches Vinylpyrrolidon-Copolymer kombiniert sind mit einem Lösungsmittel und einem Eindickungsmittel zur Generierung einer gelierten Mischung/Zubereitung.

Revendications

- 35 1. Composition pour administration transdermique retardée d'au moins un oestrogène, comprenant une base de pommade, un gel ou un film comprenant au moins un oestrogène et un copolymère de la vinylpyrrolidone insoluble dans l'eau contenant au moins 10 % en poids de vinylpyrrolidone, la concentration de l'oestrogène étant de 0,01 % à 1 % du poids total de la composition.
- 40 2. Composition selon la revendication 1, dans laquelle ledit au moins un oestrogène comprend un oestrogène choisi parmi l'estradiol, l'éthylestradiol et les esters d'estradiol et, dans laquelle le copolymère de la vinylpyrrolidone insoluble dans l'eau est non réticulé.
- 45 3. Composition selon la revendication 1 ou 2, dans laquelle le copolymère de la vinylpyrrolidone contient des motifs dérivant d'un acide insaturé choisi parmi l'acide acrylique, l'acide méthacrylique, l'acide crotonique, l'acide maléique et les anhydrides correspondants.
- 50 4. Composition selon la revendication 3, dans laquelle l'ester est choisi parmi les esters acryliques des alcanols linéaires en C₁ à C₄₀, les esters acryliques des alcanols ramifiés en C₁ à C₄₀, les esters méthacryliques des alcanols linéaires en C₁ à C₄₀ et les esters méthacryliques des alcanols ramifiés en C₁ à C₄₀.
5. Composition selon la revendication 4, dans laquelle l'ester est le méthacrylate de lauryle ou l'acrylate de 2-éthylhexyle.
- 55 6. Composition selon la revendication 2, dans laquelle ledit copolymère de la vinylpyrrolidone comprend des motifs dérivant d'un ester d'un acide saturé choisi parmi les esters vinyliques et allyliques des acides carboxyliques en C₁ à C₄₀.

7. Composition selon la revendication 6, dans laquelle l'ester est l'acétate de vinyle.
8. Composition selon la revendication 2, dans laquelle le copolymère de la vinylpyrrolidone comprend de la vinylpyrrolidone et du styrène.
- 5 9. Composition selon l'une quelconque des revendications 1, 2, 3 ou 6, dans laquelle l'oestrogène et le copolymère de la vinylpyrrolidone insoluble dans l'eau sont combinés à une base de pommade.
- 10 10. Bandage, gaz ou bande imprégné ou revêtu de la composition selon l'une quelconque des revendications précédentes.
11. Composition selon l'une quelconque des revendications 1, 2 ou 6, dans laquelle l'oestrogène et le copolymère de la vinylpyrrolidone insoluble dans l'eau sont combinés à un solvant et à un épaississant pour donner une composition gélifiée.

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